Group IV: Claims 40-48, 51, and 52, as drawn to a method of modulating the level of endogenous active CETP in a mammal comprising administering to the mammal a whole, non-endogenous CETP from an allelic variant of the mammal's endogenous CETP.

Group V: Claims 40-48, 51, and 52, as drawn to a method of modulating the level of endogenous active CETP in a mammal comprising administering to the mammal a whole, non-endogenous CETP from a mammalianized, non-endogenous CETP in which the amino acid sequence of a non-endogenous CETP has been altered by deletion or substitution of one or more amino acids.

Group VI: Claims 40-45 and 49-52, as drawn to a method of modulating the level of endogenous active CETP in a mammal comprising administering to the mammal a plasmid-based vaccine.

For Groups III-V, the Examiner dismantled the Markush group of Applicants' Claim 47, which is directed to the methods of Claims 40-45 using any of a list of preferred examples of non-endogenous CETP molecules.

With respect to the grouping of the claims, the Examiner stated:

> "4. The inventions listed as Groups I-VI above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
>
> "Ha *et al* (Biochemica et Biophysica Acta 833: 203-210, 1985; PTO 1449) teach a method for modulating the level of **endogenous** cholesteryl ester transfer protein (CETP) in a rat, which is a mammal, comprising administering to the rat a whole exogenous lipid transfer protein from human, which is non-endogenous CETP, that reduces cholesteryl ester transfer activity to about 20% at 24 hour as recited in claim 40 (See page 204 Method; page 208, Discussion in particular).
>
> **"Since Applicant's Inventions do not contribute a special technical feature when viewed over the prior art, Groups I-VI are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept and therefore lack unity of invention.**
>
> "5. Because these inventions are distinct for the reasons given above and **the searches are not coextensive**, restriction for examination purposes as indicated is proper."

Office Action (Paper No. 6), pp. 2-3 (bold emphasis added). For the reasons explained below, Applicants respectfully traverse the restriction of the claims because restriction is not proper under PCT Rules 13.1 and 13.2 or the U.S. Patent Office's own standards for searching an invention.

The Ha et al. (*Biochim. Biophys. Acta, 833*: 203-205 (1985)) Reference

First, Applicants note that persons skilled in this art are well aware that mice and rats normally lack a detectable, endogenous CETP and exhibit little if any significant background cholesteryl ester transfer (neutral lipid transfer) activity (see, p. 3, lines 14-17 of the specification; Ha et al., *Comp. Biochem. Physiol., 71B*: 265-269 (1982), copy in Tab A; paragraph bridging pp. 203-204 of Ha et al., *Biochim. Biophys. Acta, 833*: 203-205 (1985), of record; p. 257 of Gavish et al., *J. Lipid Res., 28*: 257-267 (1987), of record; Tsutsumi et al., *Biol. Pharm. Bull. 24(5)*: 579-581 (2001), copy in Tab B). In fact, it is precisely because of the deficiency of an endogenous CETP that researchers such as Ha et al. (1985) have conducted studies in rats. The aim in Ha et al. (1985) was to study any change in lipoprotein levels that would occur in rat plasma using an exogenous CETP administered at levels similar to human plasma. Ha et al. only monitored the transient level of the **non-endogenous** (exogenously provided) human CETP in the rat plasma, and Ha et al. reported that the exogenously provided **human** CETP did not persist in the rat blood: i.e., only within the first 24 hours after injecting the rats was the level of the exogenously added human CETP between 70-90% of human plasma (see, first paragraph of Results, p. 206; first paragraph of Discussion, pp. 208-209 in Ha et al. (1985)). Only by determining the half-life of the exogenously provided human CETP from the rat plasma could Ha et al. determine when to take plasma samples under conditions that approximated CETP activity in human plasma. Hence, Ha et al. do not describe a method of administering an non-endogenous CETP for the purpose of reducing endogenous CETP activity below the level of the **untreated** mammal or of modulating lipoproteins to unexpected levels. In fact, it is clear that Ha et al. would have preferred that the CETP activity never decreased in the rat plasma over time, as that would permit a system even more similar to human plasma in which CETP is constitutively produced.

Furthermore, the experimental method described in Ha et al. (1985) provides results that are **opposite** of what Applicants' invention provides, i.e., Ha et al. administered human CETP to rats to **increase** plasma CETP activity, which resulted in a **decreased** level of HDL-cholesterol and an accompanying **increased** level of LDL-cholesterol (see, Results at pp. 206-207 and Fig. 2 of Ha et al. (1985)). In Applicants' invention, a non-endogenous CETP is administered to a mammal to cause an immune response against the mammal's own, endogenous CETP which in turn **decreases** (endogenous) CETP activity, **increases** the level of HDL-cholesterol, and **decreases** the level of LDL-cholesterol to unexpected levels.

Furthermore, Ha et al. (1985) does not disclose Applicants' humanized rabbit CETP molecules comprising SEQ ID NOS:5 and 6, which are useful in the methods of the invention, or the particular embodiment of Applicants' methods wherein a non-endogenous CETP is administered to a mammal using a plasmid vector encoding the non-endogenous CETP.

The above comments clearly show that Ha et al. (1985) neither teaches nor suggests Applicants' claimed invention of administering a non-endogenous CETP to a mammal to decrease the level of the mammal's own endogenous CETP and to achieve desirable and unexpected levels of lipoproteins.

The Invention and PCT Rules 13.1 and 13.2

As a national stage of PCT/US98/22145, the standard for restricting claims of this application into separate inventions is found in PCT Rules 13.1 and 13.2.

PCT Rule 13.1 states that:

> "The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept."

PCT Rule 13.2 states that:

> "Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only **when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features**. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

Applicants' claimed invention provides compositions and methods for modulating the level of endogenous CETP and the circulating levels of HDL- and LDL-cholesterol in a mammal. All of the claimed methods (Claims 40-52) comprise the **same technical feature** of administering to a mammal a whole, **non-endogenous** CETP (i.e., a CETP molecule that is not the native CETP produced by the mammal) to alter the level of the mammal's **endogenous** CETP or lipoprotein-associated cholesterol to unexpected levels as recited in the claims (e.g., CETP activity below 20% of the **untreated** mammal, 0 μg of CETP in the blood, greater than about 90% of cholesterol as HDL-cholesterol, less than about 10% of cholesterol as LDL-cholesterol). Claim 49 is directed to the particular embodiment of the methods in which the non-endogenous CETP is administered to the mammalian subject using a plasmid, which encodes and expresses the non-endogenous CETP. Claims 38 and 39 are directed to specific humanized rabbit CETP molecules that are clearly non-endogenous CETP, as neither are known to exist in any mammal.

Applicants respectfully submit that PCT Rules 13.1 and 13.2 are clearly fulfilled, because there clearly is a "single general inventive concept" (PCT Rule 13.1) in all of the claims. A "technical relationship" exists that involves the same "special technical feature" of employing a non-endogenous CETP molecule to modulate a mammal's own endogenous CETP or lipoprotein profile in the blood to

heretofore unknown and unexpected levels. Accordingly, as the conditions of PCT Rules 13.1 and 13.2 for unity of invention are fulfilled by Claims 38-52, election of a restriction group is improper.

Criteria for Searching Inventions

Finally, Applicants note that the Patent Office's own criteria for searching inventions are also consistent with prosecuting Claims 38-52 in a single application.

Proper restriction between independent and distinct inventions claimed in the same application requires (1) that the inventions must be independent and distinct as claimed, AND (2) that there must be a serious burden placed on the Examiner by not requiring restriction. If either criterion is not met, restriction is not proper.

> **IF THE SEARCH AND EXAMINATION OF AN ENTIRE APPLICATION CAN BE MADE WITHOUT SERIOUS BURDEN, THE EXAMINER MUST EXAMINE IT ON THE MERITS, EVEN THOUGH IT INCLUDES CLAIMS TO INDEPENDENT OR DISTINCT INVENTIONS. MANUAL OF PATENT EXAMINING PROCEDURE (MPEP) § 803.**

Current federal regulations and guidelines directed to patent applications provide for the examination in one application of product and method claims, even where distinct inventions exist, if the inventions are related. Such is the case here. The subject matter of Applicants' invention is directed to the use of a non-endogenous CETP molecule to modulate a mammal's own endogenous CETP and lipoprotein profile to heretofore unexpected and unknown levels. The humanized rabbit CETP molecules of Claims 38 and 39 are heretofore unknown CETP molecules that are clearly not endogenous CETP to **any known mammal**. Claim 49 is a particular embodiment of the methods of the invention wherein a non-endogenous CETP is administered to a mammal using a plasmid vector instead of the non-endogenous protein *per se* (see, p. 13, lines 10-18; p. 20, line 26-p. 22, line 7; Fig. 14 of the specification).

Because the claims of the present invention are directed to novel methods of modulating endogenous CETP in a mammal comprising administering a non-endogenous CETP molecule and to two examples of novel, non-endogenous CETP molecules useful in such methods, Applicants respectfully submit that search and examination of the subject matter would not place a serious burden on the Examiner. In the absence of a serious burden, the Examiner MUST examine the application on the merits, irrespective of the presence of claims to independent and distinct inventions. Accordingly, the restriction of Claims 38-52 is improper under the practice of the Patent Office promulgated in the MPEP.

Conclusion and Provisional Election

Applicants respectfully submit that, in view of the foregoing remarks, Claims 38-52 are seen to be related by a technical relationship involving one or more of the same or corresponding special technical features as required by PCT Rules 13.1 and 13.2. Furthermore, a search for the subject matter of the claims would not unduly burden the Examiner, as the claims are related to a single inventive concept, are derived from a single inventive effort, and are in a form and are of the sort that is properly viewed as relating to a single invention that should not be restricted. Accordingly, Applicants respectfully request that the election of one of Restriction Groups I-VI of the Office Action of September 21, 2001 be reconsidered and withdrawn.

Although Applicants believe that the restriction and the requirement of election are improper, and without in any way acquiescing to the reasons for the requirements set forth in the Office Action, but in order to be fully responsive to the Office Action, Applicants provisionally elect for examination the claims of Group III.

Respectfully submitted,

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CERTIFICATE OF MAILING PURSUANT TO 37 C.F.R. § 1.10

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October 22, 2001
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